UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,071	02/25/2004	Robert E. Dudley	04251764	2849

26565 7590 05/29/2008

MAYER BROWN LLP
P.O. BOX 2828
CHICAGO, IL 60690

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
05/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/787,071	DUDLEY, ROBERT E.	
	Examiner	Art Unit	
	KENDRA D. CARTER	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *1-31,51 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-50 and 53-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of April 8, 2008 made to the office action filed October 2, 2007. Claims 1-71 are pending. Claims 32, 35, 38, 39, 43, 45-46 and 48 are amended and claims 53-71 are new.

In light of the amendments, the following rejections are withdrawn: 1) the obviousness-type double patenting rejection of claims 32, 39-42, 45, 46 and 50 as being unpatentable over copending Application No. 10/825,540 in view of Reed et al.; 2) the obviousness-type double patenting rejection of claims 32, 39-42, 45, 46 and 50 as being unpatentable over copending Application No. 10/828,678 in view of Reed et al.; 3) the obviousness-type double patenting rejection of claims 32, 40-42, 45, and 47 as being unpatentable over copending Application No. 10/828,678 in view of Reed et al.; and 4) the 35 USC 112, second paragraph rejections of claims 39, 43 and 44.

For the reasons in the previous office action and below, the Applicant's arguments of the following rejections were found not persuasive and thus are maintained: 1) the 35 USC 103(a) rejection of claims 32, 35, 37-45, 47, 49 and 50 as being unpatentable over Reed et al., Dittgen et al., and in further view of Kim et al.; 2) the 35 USC 103(a) rejection of claims 33 and 48 as being unpatentable over Reed et al., Dittgen et al., and in further view of Kim et al. as applied to claims 32, 35, 37-45, 47, 49 and 50, in further view of Wang et al.; 3) the 35 USC 103(a) rejection of claims 34

and 36 as being unpatentable over Reed et al., Dittgen et al., and in further view of Kim et al. as applied to claims 32, 35, 37-45, 47, 49 and 50, in further view of Doherty, Jr. et al.; and 4) the 35 USC 103(a) rejection of claim 46 as being unpatentable over Reed et al., Dittgen et al., and in further view of Kim et al. as applied to claims 32, 35, 37-45, 47, 49 and 50, in further view of Dobs et al.

Due to the amendment to the claims, the modified and new 35 USC 103(a) rejections are made below. Applicant's arguments are addressed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

(1) Claims 32, 36-45, 47, 49 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al. (US 6,299,900 B1) in view of Dittgen et al. (US 6,238,284 B1), in further view of Kim et al. (US 5,482,970).

Reed et al. teach a precutaneous or transdermal drug delivery system for humans (see abstract, lines 1-15) comprising at least one physiologically active agent such as papaverine (i.e. pharmaceutical useful drug for treating erectile dysfunction; see column 5, line 31; addresses claims 32), alprostadil (i.e. pharmaceutical useful drug for treating erectile dysfunction; see claim 21), phentolamine (i.e. pharmaceutical useful drug for treating erectile dysfunction, see column 5, line 31; addresses claim 32), or preferably testosterone (i.e. pharmaceutical useful drug for treating erectile dysfunction, see column 14, line 59 and claim 21; addresses claims 32, 40, 41, and 49), at least one volatile liquid such as ethanol (see column 11, line 21; addresses claims 32, 39 and 44) and a penetration enhancer such as oleic acid (column 10, line 58; addresses claims 37 and 38) or isopropyl myristate (see column 10, lines 63 and 64 and abstract, lines 1-10; addresses claims 32, 40, 42 and 44). Reed et al. teaches that some major problems with the current state of the art relate to a lack of efficacy of systemic drugs because of the low drug flux across the skin (see column 1, lines 28-31; addresses claim 32). Transdermal systemic drug delivery provides an effective method of achieving improved bioavailability for physiologically active substances where the drugs are poorly absorbed by traditional routes of delivery (see column 1, lines 48-51; addresses claim 32). The isopropyl myristate and ethanol may be used in range of 1 to 50%. Because of the

effect of the penetration enhancer, the dosage of the physiologically active agent may often be less than that conventionally used. The concentration of physiologically active agents used in the drug delivery system will depend on its properties and may be equivalent to that normally utilized for the particular agent in conventional formulations. Both the amount of the physiologically active agent and the amount of penetration enhancer will be influenced by the type of effect desired (see column 11, lines 66-67 and column 12, lines 1-2 and 6-11; addresses claims 41, 44 and 49). The ratio of penetration enhancer to active ingredient may vary considerably and will be governed as much as anything, by the pharmacological results that are required to be achieved. In principle, it is desirable that as little absorption enhancer as possible is used (see column 12, lines 26-30; addresses claims 41, 44 and 49). The method may be applied to treat any appropriate disease or condition (see column 15, lines 38-39; addresses claims 32, 33, 45 and 46). Figure 9 shows the predicted testosterone plasma concentration in hypogonadal males after once daily dosing to steady state with a metered dose (see column 16, lines 37-40; addresses claims 45, 47 and 50)

Reed et al. does not specifically teach a method for improving the efficacy of a pharmaceutical useful for treating erectile dysfunction (claim 32), carbopol, or the specific amounts of the testosterone, isopropyl myristate, carbopol, and ethanol (claims 41, 44 and 49).

Dittgen et al. teach a transdermal therapeutic system for application to the skin and/or mucosa consisting of at least one active substance such as testosterone in amounts of 0.5%, 0.50 g (column 10, lines 1 and 7), or 8.4 mg (see column 12, line 16) in combination with at least one destructing agent and/or at least one structuring agent in a common matrix (see abstract). The composition also comprises a penetration enhancer such as oleic acid and isopropyl myristate from the region of 0 to 1.4% or at least 2% (see column 7, lines 6-8, 41 and 42), carbopol in an amount of 0.5 g and ethanol in an amount of 46.87 g (see column 10, lines 8 and 10).

Kim et al. teaches that the control of the rate and extent of membrane penetration and degree of metabolic conversion is achieved by selecting a vehicle comprising the appropriate polar organic solvent and metabolism modulator, and varying the proportion of polar organic solvent and metabolism modulator in the vehicle. Thus, for example, control of the rate and extent of membrane penetration and degree of metabolic conversion is achieved by employing isoproyl myristate and ethanol (see column 2, lines 40-45 and column 9, lines 35-37). A greater efficacy of inocoterone acetate when applied in the isopropyl myristate-ethanol mixture was observed and was consistent with the increased transcutaneous penetration observed (see column 9, lines 35-37 and Example 3). The transdermal composition of Kim et al. also comprises carbopol as a viscosity-increasing agents at 0.7 wt/wt (see column 4, lines 29 and 31; example 12).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine Reed et al. and the specific method for improving the efficacy of a pharmaceutical useful for treating erectile dysfunction because first, Reed et al. teach drugs that treat erectile dysfunction. Second, Reed et al. teaches that a lack of efficacy of systemic drugs because of the low drug flux across the skin (see column 1, lines 28-31), and transdermal systemic drug delivery provides an effective method of achieving improved bioavailability for physiologically active substances (see column 1, lines 48-51). Third, Kim et al. teach that a greater efficacy of inocoterone acetate when applied in the isopropyl myristate-ethanol mixture was observed and was consistent with the increased transcutaneous penetration observed (see column 9, lines 35-37 and Example 3). Thus, by delivering the drug through a drug delivery system of Reed et al., and the specific penetration enhancers isopropyl myristate and ethanol will increase penetration of the drug through the skin and thus improve the efficacy.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine Reed et al. and carbopol is because of the following teachings: 1) Reed et al., Dittgen et al. and Kim et al. all teach transdermal pharmaceutical formulations that all contain penetration enhancers; 2) Dittgen et al. teach carbopol in an amount of 0.5 g (see column 10, lines 8 and 10); 3) Kim et al. teach carbopol as a viscosity-increasing agents at 0.7 wt/wt (see column 4, lines 29 and 31; example 12); and 4) "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third

composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987). Thus, one skilled in the art would be motivated to add carbopol to the composition of Reed et al. because it has been shown in the art that carbopol is used in other transdermal applications with penetration enhancers.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine Reed et al. and the specific amounts of the testosterone, isopropyl myristate, carbopol, and ethanol because of the following teachings: 1) Reed et al., Dittgen et al. and Kim et al. all teach transdermal pharmaceutical formulations that all contain penetration enhancers; 2) Dittgen et al. teach testosterone in amounts of 0.5%, 0.50 g (column 10, lines 1 and 7), or 8.4 mg (see column 12, line 16), penetration enhancer such as oleic acid and isopropyl myristate from the region of 0 to 1.4% or at least 2% (see column 7, lines 6-8, 41 and 42), carbopol in an amount of 0.5 g and ethanol in an amount of 46.87 g (see column 10, lines 8 and 10); 3) Kim et al. teach carbopol as a viscosity-increasing agents at 0.7 wt/wt (see column 4, lines 29 and 31; example 12); 4) Reed et al. teach isopropyl myristate and ethanol may be used in range of 1 to 50%; 5) Reed et al. also teach that because of the effect of the penetration enhancer, the dosage of the physiologically

active agent may often be less than that conventionally used; the concentration of physiologically active agents used in the drug delivery system will depend on its properties and may be equivalent to that normally utilized for the particular agent in conventional formulations; and both the amount of the physiologically active agent and the amount of penetration enhancer will be influenced by the type of effect desired (see column 11, lines 66-67 and column 12, lines 1-2 and 6-11); 6) Reed et al. also teach that the ratio of penetration enhancer to active ingredient may vary considerably and will be governed as much as anything, by the pharmacological results that are required to be achieved; and in principle, it is desirable that as little absorption enhancer as possible is used (see column 12, lines 26-30); 7) It is the normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages. See In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("[D]iscovery of an optimum value of the result effective variable in a known process is ordinarily within the skill of the art." See, e.g., In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *In re Paterson* Appeal No. 02-1189 (Fed. Cir. January 8, 2003). Thus, one skilled in the art would be able to adjust the ranges of testosterone, isopropyl myristate, carbopol, and ethanol because of the different amounts provided in prior art such as Reed et al., Dittgen et al. and Kim et al. to achieve the desired pharmacological results.

(2) Claims 33, 48, 53 and 56-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al. (US 6,299,900 B1) in view of Dittgen et al. (US 6,238,284 B1), in further view of Kim et al. (US 5,482,970) as applied to claims 32, 36-45, 47, 49 and 50 above, in further view of Wang et al. (Journal of Clinical Endocrinology and Metabolism, August 1998, vol. 83(8), pp. 2749-2757).

The teachings of Reed et al., Dittgen et al. and Kim et al. are as applied to claims 32, 36-45, 47, 49 and 50.

Reed et al., Dittgen et al. and Kim et al. do not teach wherein the subject is eugonadal (claims 33 and 53) and wherein the delivery comprises administering the composition to the right/left upper arms/shoulders and to the right/left sides of the abdomen once per day on alternate days (claim 48).

Wang et al. teach comparative pharmacokinetics of three doses of percutaneous dihydrotestosterone (DHT) gel in men (see title). The DHT was administered daily over one upper arm; both arms and shoulders; and bilateral arms, shoulders and upper abdomen (see abstract, lines 3-6; addresses claim 48). The serum DHT was maintained at stable levels both in hypogonadal and egonadal men (see page 2750, column 1, lines 1-2; addresses claim 33).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Reed et al., in view of Dittgen et al., in further view of Kim et al. and wherein the subject is eugonadal because Wang et al. teaches that transdermal applications of a testosterone derivative was effective in maintaining stable levels of serum DHT in eugonadal men. Thus, one would be motivated to combine the method of Reed et al. with eugonadal men because of the expectation of success that the penetration enhancers would increase the efficacy of the drug useful for treating erectile dysfunction and testosterone as taught by Reed et al., Kim et al. and Wang et al. Additionally, Reed et al. teach that the method may be applied to treat any appropriate disease or condition (see column 15, lines 38-39).

(3) Claims 34 and 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al. (US 6,299,900 B1) in view of Dittgen et al. (US 6,238,284 B1), in further view of Kim et al. (US 5,482,970) as applied to claims 32, 36-45, 47, 49 and 50 above, in further view of Doherty, Jr. et al. (US 6,037,346)

The teachings of Reed et al., Dittgen et al. and Kim et al. are as applied to claims 32, 36-45, 47, 49 and 50.

Reed et al., Dittgen et al. and Kim et al. do not teach a phosphodiesterase type 5 inhibitor(claim 34) or VIAGRA, UPRIMA, TRENTAL or ACTIBINE (claim 36).

Doherty, Jr. et al. teach local administration of phosphodiesterase inhibitors, preferably type V (see column 3, lines 66-67) for the treatment of erectile dysfunction (see title; addresses claim 34). The drug is delivered transdermally, which includes percutaneous administration (see column 4, line 60 and column 6, lines 22-23). Various compounds are known as inhibitors of phosphodiesterases including sildenafil citrate (VIAGRA; see column 3, lines 21-22 and 25; addresses claim 36)

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Reed et al., in view of Dittgen et al., in further view of Kim et al. and a phosphodiesterase type 5 inhibitor or VIAGRA is because Doherty, Jr. et al. teach percutaneous administration of phosphodiesterase type 5 inhibitor such as VIAGRA for the treatment of erectile dysfunction (see column 3, lines 21-22 and 25 and title). Thus, one would be motivated to combine the method of Reed et al. with a phosphodiesterase type 5 inhibitor or VIAGRA because of the expectation of success that the penetration enhancers would increase the efficacy of the drug as taught by Reed et al. and Kim et al.

(4) Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al. (US 6,299,900 B1) in view of Dittgen et al. (US 6,238,284 B1), in further view of Kim et al. (US 5,482,970) as applied to claims 32, 36-45, 47, 49 and 50

above, in further view of Dobs et al. (The Journal of Clinical Endocrinology and Metabolism, October 1999, vol. 84(10), pp. 3469-3478)

The teachings of Reed et al., Dittgen et al. and Kim et al. are as applied to claims 32, 36-45, 47, 49 and 50.

Reed et al., Dittgen et al. and Kim et al. do not teach wherein the man suffers from primary hypogonadism.

Dobs et al. teach pharmacokinetics, efficacy and safety of a permeation-enhance testosterone transdermal system (TDD) in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men (see title). Both treatments are efficacious for replacing testosterone in hypogonadal men, the more physiological sex hormone levels and profiles associated with TDD may offer possible advantages over intramuscular injections (see abstract, column 2, last paragraph). Out of the 33 male patients treated, 10 or 30.3 % were primary hypogonadal and 23 or 69.7% were secondary hypogonadal (see page 3471, table 1).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Reed et al., in view of Dittgen et al., in further view of Kim et al. and wherein the subject suffers from primary hypogonadism because Dobs et al. teaches that transdermal applications have more advantages then

injections of testosterone for the treatment of primary hypogonadal men (see abstract, column 2, last paragraph and see page 3471, table 1). Thus, one would be motivated to combine the method of Reed et al. with primary hypogonadism men because of the expectation of success that the penetration enhancers would increase the efficacy of the drug as taught by Reed et al. and Kim et al. Additionally, Reed et al. teach that the method may be applied to treat any appropriate disease or condition (see column 15, lines 38-39), and showed the predicted testosterone plasma concentration in hypogonadal males after once daily dosing to steady state with a metered dose (see column 16, lines 37-40 and Figure 9).

(5) Claims 54 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al. (US 6,299,900 B1) in view of Dittgen et al. (US 6,238,284 B1), in further view of Kim et al. (US 5,482,970) as applied to claims 32, 36-45, 47, 49 and 50 above, in further view of Wang et al. (Journal of Clinical Endocrinology and Metabolism, August 1998, vol. 83(8), pp. 2749-2757) as applied to claims 33, 48, 53 and 56-62 above, in further view of Doherty, Jr. et al. (US 6,037,346)

The teachings of Reed et al., Dittgen et al., Kim et al., and Wang et al. are as applied to claims 32, 33, 36-45, 47-50, 53 and 56-72 above.

Reed et al., Dittgen et al., Kim et al. and Wang et al. do not teach a phosphodiesterase type 5 inhibitor or VIAGRA, UPRIMA, TRENTAL or ACTIBINE.

Doherty, Jr. et al. teach local administration of phosphodiesterase inhibitors, preferably type V (see column 3, lines 66-67) for the treatment of erectile dysfunction (see title; addresses claim 34). The drug is delivered transdermally, which includes percutaneous administration (see column 4, line 60 and column 6, lines 22-23). Various compounds are known as inhibitors of phosphodiesterases including sildenafil citrate (VIAGRA; see column 3, lines 21-22 and 25; addresses claims 54 and 55)

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Reed et al., in view of Dittgen et al., in further view of Kim et al. and a phosphodiesterase type 5 inhibitor or VIAGRA is because Doherty, Jr. et al. teach percutaneous administration of phosphodiesterase type 5 inhibitor such as VIAGRA for the treatment of erectile dysfunction (see column 3, lines 21-22 and 25 and title) Thus, males including those who are eugonadal or suffer from hypogonadism with erectile dysfunction would be treated, because VIAGRA treats the erectile dysfunction, while the efficacy of VIAGRA would obviously improved by the penetration enhancers as taught by Reed et al. and Kim et al.

(6) Claims 63-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al. (US 6,299,900 B1) in view of Dittgen et al. (US 6,238,284 B1), in further view of Kim et al. (US 5,482,970), in further view of Doherty, Jr. et al. (US 6,037,346)

Reed et al. teach a precutaneous or transdermal drug delivery system for humans (see abstract, lines 1-15) comprising at least one physiologically active agent such as papaverine (i.e. pharmaceutical useful drug for treating erectile dysfunction; see column 5, line 31), alprostadil (i.e. pharmaceutical useful drug for treating erectile dysfunction; see claim 21), phentolamine (i.e. pharmaceutical useful drug for treating erectile dysfunction, see column 5, line 31), or preferably testosterone (i.e. pharmaceutical useful drug for treating erectile dysfunction, see column 14, line 59 and claim 21; addresses claims 63 and 70), at least one volatile liquid such as ethanol (see column 11, line 21; addresses claims 63, 67 and 70) and a penetration enhancer such as oleic acid (column 10, line 58; addresses claims 63 and 66) or isopropyl myristate (see column 10, lines 63 and 64 and abstract, lines 1-10; addresses claims 63, 68 and 70). Reed et al. teaches that some major problems with the current state of the art relate to a lack of efficacy of systemic drugs because of the low drug flux across the skin (see column 1, lines 28-31; addresses claim 63). Transdermal systemic drug delivery provides an effective method of achieving improved bioavailability for physiologically active substances where the drugs are poorly absorbed by traditional routes of delivery (see column 1, lines 48-51; addresses claim 63). The isopropyl myristate and ethanol may be used in range of 1 to 50%. Because of the effect of the penetration enhancer, the dosage of the physiologically active agent may often be less than that conventionally used. The concentration of physiologically active agents used in the drug delivery system will depend on its properties and may be equivalent to that

normally utilized for the particular agent in conventional formulations. Both the amount of the physiologically active agent and the amount of penetration enhancer will be influenced by the type of effect desired (see column 11, lines 66-67 and column 12, lines 1-2 and 6-11; addresses claim 70). The ratio of penetration enhancer to active ingredient may vary considerably and will be governed as much as anything, by the pharmacological results that are required to be achieved. In principle, it is desirable that as little absorption enhancer as possible is used (see column 12, lines 26-30; addresses claim 70). The method may be applied to treat any appropriate disease or condition (see column 15, lines 38-39; addresses claim 70).

Reed et al. does not specifically teach a method for improving the efficacy of a pharmaceutical useful for treating erectile dysfunction (claim 63), carbopol (claim 69), or the specific amounts of the testosterone, isopropyl myristate, carbopol, and ethanol (claim 70). Reed et al. also does not teach a phosphodiesterase type 5 inhibitor (claim 63), particularly, VIAGRA, UPRIMA, TRENTAL or ACTIBINE (claim 64).

Dittgen et al. teach a transdermal therapeutic system for application to the skin and/or mucosa consisting of at least one active substance such as testosterone in amounts of 0.5%, 0.50 g (column 10, lines 1 and 7), or 8.4 mg (see column 12, line 16) in combination with at least one destructing agent and/or at least one structuring agent in a common matrix (see abstract). The composition also comprises a penetration enhancer such as oleic acid and isopropyl myristate from the region of 0 to 1.4% or at

least 2% (see column 7, lines 6-8, 41 and 42), carbopol in an amount of 0.5 g and ethanol in an amount of 46.87 g (see column 10, lines 8 and 10).

Kim et al. teaches that the control of the rate and extent of membrane penetration and degree of metabolic conversion is achieved by selecting a vehicle comprising the appropriate polar organic solvent and metabolism modulator, and varying the proportion of polar organic solvent and metabolism modulator in the vehicle. Thus, for example, control of the rate and extent of membrane penetration and degree of metabolic conversion is achieved by employing isoproyl myristate and ethanol (see column 2, lines 40-45 and column 9, lines 35-37). A greater efficacy of inocoterone acetate when applied in the isopropyl myristate-ethanol mixture was observed and was consistent with the increased transcutaneous penetration observed (see column 9, lines 35-37 and Example 3). The transdermal composition of Kim et al. also comprises carbopol as a viscosity-increasing agents at 0.7 wt/wt (see column 4, lines 29 and 31; example 12).

Doherty, Jr. et al. teach local administration of phosphodiesterase inhibitors, preferably type V (see column 3, lines 66-67) for the treatment of erectile dysfunction (see title; addresses claim 34). The drug is delivered transdermally, which includes percutaneous administration (see column 4, line 60 and column 6, lines 22-23). Various compounds are known as inhibitors of phosphodiesterases including sildenafil citrate (VIAGRA; see column 3, lines 21-22 and 25)

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Reed et al., in view of Dittgen et al., in further view of Kim et al. and a phosphodiesterase type 5 inhibitor or VIAGRA is because Doherty, Jr. et al. teach percutaneous administration of phosphodiesterase type 5 inhibitor such as VIAGRA for the treatment of erectile dysfunction (see column 3, lines 21-22 and 25 and title). Thus, one would be motivated to combine the method of Reed et al. with a phosphodiesterase type 5 inhibitor or VIAGRA because of the expectation of success that the penetration enhancers would increase the efficacy of the drug as taught by Reed et al. and Kim et al.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine Reed et al. and the specific method for improving the efficacy of a pharmaceutical useful for treating erectile dysfunction because first, Reed et al. teach drugs that treat erectile dysfunction. Second, Reed et al. teaches that a lack of efficacy of systemic drugs because of the low drug flux across the skin (see column 1, lines 28-31), and transdermal systemic drug delivery provides an effective method of achieving improved bioavailability for physiologically active substances (see column 1, lines 48-51). Third, Kim et al. teach that a greater efficacy of inocoterone acetate when applied in the isopropyl myristate-ethanol mixture was observed and was consistent with the increased transcutaneous penetration observed (see (see column 9, lines 35-37 and Example 3). Thus, by delivering the drug through a drug delivery system of

Reed et al., and the specific penetration enhancers isopropyl myristate and ethanol will increase penetration of the drug through the skin and thus improve the efficacy.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine Reed et al. and carbopol is because of the following teachings: 1) Reed et al., Dittgen et al. and Kim et al. all teach transdermal pharmaceutical formulations that all contain penetration enhancers; 2) Dittgen et al. teach carbopol in an amount of 0.5 g (see column 10, lines 8 and 10); 3) Kim et al. teach carbopol as a viscosity-increasing agents at 0.7 wt/wt (see column 4, lines 29 and 31; example 12); and 4) "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987). Thus, one skilled in the art would be motivated to add carbopol to the composition of Reed et al. because it has been shown in the art that carbopol is used in other transdermal applications with penetration enhancers.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine Reed et al. and the specific amounts of the

testosterone, isopropyl myristate, carbopol, and ethanol because of the following teachings: 1) Reed et al., Dittgen et al. and Kim et al. all teach transdermal pharmaceutical formulations that all contain penetration enhancers; 2) Dittgen et al. teach testosterone in amounts of 0.5%, 0.50 g (column 10, lines 1 and 7), or 8.4 mg (see column 12, line 16), penetration enhancer such as oleic acid and isopropyl myristate from the region of 0 to 1.4% or at least 2% (see column 7, lines 6-8, 41 and 42), carbopol in an amount of 0.5 g and ethanol in an amount of 46.87 g (see column 10, lines 8 and 10); 3) Kim et al. teach carbopol as a viscosity-increasing agents at 0.7 wt/wt (see column 4, lines 29 and 31; example 12); 4) Reed et al. teach isopropyl myristate and ethanol may be used in range of 1 to 50%; 5) Reed et al. also teach that because of the effect of the penetration enhancer, the dosage of the physiologically active agent may often be less than that conventionally used; the concentration of physiologically active agents used in the drug delivery system will depend on its properties and may be equivalent to that normally utilized for the particular agent in conventional formulations; and both the amount of the physiologically active agent and the amount of penetration enhancer will be influenced by the type of effect desired (see column 11, lines 66-67 and column 12, lines 1-2 and 6-11); 6) Reed et al. also teach that the ratio of penetration enhancer to active ingredient may vary considerably and will be governed as much as anything, by the pharmacological results that are required to be achieved; and in principle, it is desirable that as little absorption enhancer as possible is used (see column 12, lines 26-30); 7) It is the normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to

determine where in a disclosed set of percentage ranges is the optimum combination of percentages. See In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("[D]iscovery of an optimum value of the result effective variable in a known process is ordinarily within the skill of the art." See, e.g., In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *In re Paterson* Appeal No. 02-1189 (Fed. Cir. January 8, 2003). Thus, one skilled in the art would be able to adjust the ranges of testosterone, isopropyl myristate, carbopol, and ethanol because of the different amounts provided in prior art such as Reed et al., Dittgen et al. and Kim et al. to achieve the desired pharmacological results.

(7) Claim 53-59 and 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al. (US 6,342,246) in view of Reed et al. (US 6,299,900 B1)

Johnson et al. teach a fast-dispersing oral composition comprising active ingredients selected from a dopamine agonist such as apomorphine (i.e. UPRIMA; phosphodiesterase type 5 inhibitor), testosterone and mixtures thereof to treat erectile dysfunction in males (see abstract and column 2, line 32; addresses claims 53-55 and 71). The use of a fast-dispersing dosage form has the following advantages over the conventional sublingual tablet: 1) allows low doses to be employed; 2) allows the dose to be taken when it is required rather than a considerable time before sexual activity; and 3) the active ingredient is rapidly absorbed rather than absorbed over a prolonged

period of time (i.e. improving the efficacy of a pharmaceutical useful for treating erectile dysfunction; see column 2, lines 41-55; addresses claims 53 and 71).

Johnson et al. does not specifically teach treatment in eugonadal males (claim 53), isopropyl myristate (i.e. penetration enhancer; claims 53, 56, 57, 59 and 71), or ethanol (claims 53, 58 and 71). Johnson et al. also does not teach that the testosterone composition is administered percutaneously (claim 53 and 71).

Reed et al. teach a precutaneous or transdermal drug delivery system for humans (see abstract, lines 1-15) comprising at least one physiologically active agent such as testosterone (see column 14, line 59 and claim 21), at least one volatile liquid such as ethanol (see column 11, line 21) and a penetration enhancer such as oleic acid (column 10, line 58) or isopropyl myristate (see column 10, lines 63 and 64 and abstract, lines 1-10). Reed et al. teaches that some major problems with the current state of the art relate to a lack of efficacy of systemic drugs because of the low drug flux across the skin (see column 1, lines 28-31). Transdermal systemic drug delivery provides an effective method of achieving improved bioavailability for physiologically active substances where the drugs are poorly absorbed by traditional routes of delivery (see column 1, lines 48-51). The isopropyl myristate and ethanol may be used in range of 1 to 50%. Because of the effect of the penetration enhancer, the dosage of the physiologically active agent may often be less than that conventionally used. The concentration of physiologically active agents used in the drug delivery system will

depend on its properties and may be equivalent to that normally utilized for the particular agent in conventional formulations. Both the amount of the physiologically active agent and the amount of penetration enhancer will be influenced by the type of effect desired (see column 11, lines 66-67 and column 12, lines 1-2 and 6-11). The ratio of penetration enhancer to active ingredient may vary considerably and will be governed as much as anything, by the pharmacological results that are required to be achieved. In principle, it is desirable that as little absorption enhancer as possible is used (see column 12, lines 26-30; addresses claims 41, 44 and 49). The method may be applied to treat any appropriate disease or condition (see column 15, lines 38-39).

Wang et al. teach comparative pharmacokinetics of three doses of percutaneous dihydrotestosterone (DHT) gel in men (see title). The DHT was administered daily over one upper arm; both arms and shoulders; and bilateral arms, shoulders and upper abdomen (see abstract, lines 3-6). The serum DHT was maintained at stable levels both in hypogonadal and egonadal men (see page 2750, column 1, lines 1-2; addresses claim 33).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine et al. and because Reed et al. teaches that

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine Johnson et al. and wherein the testosterone

composition is administered percutaneously (claim 53 and 71) including isopropyl myristate (i.e. penetration enhancer; claims 53, 56, 57 and 59) and/or ethanol (claims 53 and 58) because Reed et al. teach drug enhancement of drugs such as testosterone in a composition that includes alcohols such as ethanol and the penetration enhancer such as isopropyl myristate. Reed et al. further teach that a lack of efficacy of systemic drugs because of the low drug flux across the skin (see column 1, lines 28-31), and transdermal systemic drug delivery provides an effective method of achieving improved bioavailability for physiologically active substances (see column 1, lines 48-51). Thus, one would be motivated to use the drug enhancement system of Reed et al. with the method of Johnson et al. with the expectation of improved bioavailability of the testosterone or the like.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Johnson et al. in view of Reed et al. and wherein the subject is eugonadal because the symptom of erectile dysfunction will be treated with compounds of Johnson et al. Additionally, one skilled in the art would have the expectation of success that the improved dosage administration forms of Johnson et al. and Reed et al. would increase the bioavailability of the active compounds to treat erectile dysfunction. Additionally, Reed et al. teach that the method may be applied to treat any appropriate disease or condition (see column 15, lines 38-39).

Response to Arguments

> The Applicant argues that as amended, the claim 32 requires a method of improving the efficacy of a pharmaceutical other than testosterone, which is useful for treating erectile dysfunction in a male subject. None of the references teach any other pharmaceutical agent used in combination with testosterone. Reed et al. or any of the other prior art does not teach how to improve the efficacy of more than one pharmaceutical, other than testosterone, useful for treating erectile dysfunction. Also, it is not obvious to combine testosterone with another pharmaceutical which is useful for treating erectile dysfunction because the Applicant achieved surprising and improved results when testosterone was combined with such a pharmaceutical on pages 47-54 of the specification.

The Examiner disagrees because Reed et al. teaches that the composition can comprise one or more physiologically active agent such as papaverine (i.e. pharmaceutical useful drug for treating erectile dysfunction; see column 5, line 31; addresses claims 32), alprostadil (i.e. pharmaceutical useful drug for treating erectile dysfunction; see claim 21), phentolamine (i.e. pharmaceutical useful drug for treating erectile dysfunction, see column 5, line 31), or testosterone (i.e. pharmaceutical useful drug for treating erectile dysfunction, see column 14, line 59 and claim 21). The motivation to combine the erectile dysfunction drugs is in the expectation to effectively treat erectile dysfunction. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also *In re*

Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987). The Examiner agrees that there is not specific example of the combination of testosterone with one of the other drugs, but a specific example is not needed when the application is taken as a whole, particularly in light of the teaching above. The improvement of efficacy is addressed by the composition as a whole as taught by Reed et al. because transdermal systemic drug delivery provides an effective method of achieving improved bioavailability for physiologically active substances (see column 1, lines 48-51). In regards to the unexpected results presented by the Applicant, the Examiner disagrees that these are unexpected results. Particularly because the Applicant only provides a prophetic example (see page 53) in which the Applicant "expects" that all test parameters will show improvement and synergy with the combination (see page 54, first paragraph). There is no empirical data showing any unexpected results of the invention. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion". Thus, "prophetic" examples are not considered as unexpected results.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 7:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/K. D. C./
Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617